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Delivery of water insoluble bioactive agents as suspended nanoparticles - by coating agent in organic phase with aqueous protein and/or synthetic polymer as stabiliser, under high shear, notable use for taxol.

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Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9814174	A1	19980409	WO 97US17157	A	19970924	199830	B
AU 9745929	A	19980424	AU 9745929	A	19970924	199835	
NO 9901620	A	19990601	WO 97US17157	A	19970924	199932	
			NO 991620	A	19990406		
US 5916596	A	19990629	US 9323698	A	19930222	199932	
			US 95412726	A	19950329		
			US 96720756	A	19961001		
EP 961612	A1	19991208	EP 97944429	A	19970924	200002	
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			JP 98516657	A	19970924		
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Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
AU 9745929	A				Based on patent WO 9814174
US 5916596	A				Div ex application US 9323698 CIP of application US 95412726 Div ex patent US 5439686 CIP of patent US 5560933
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AU 718753	B				Previous Publ. patent AU 9745929 Based on patent WO 9814174
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Abstract (Basic): WO 9814174 A

Formulation of a pharmacologically active agent, almost insoluble in water, for in vivo delivery, comprises subjecting a mixture comprising: (a) the agent dispersed in an organic phase; and (b) aqueous medium containing biocompatible polymer; to high shear conditions in a high pressure homogeniser at a pressure between 3000 and 30000 psi, provided that substantially no surfactants are present;

and, optionally, removing the organic and/or aqueous phase from the mixture. Also claimed is a drug delivery system, comprising particles of a solid or liquid, water insoluble pharmacologically active agent, coated with protein, in which the coating has associated protein; a portion of the active agent is contained within the protein coating, and a portion is associated with the protein; and the average diameter of the particles is not greater than 1 mu .

USE - The formulation produces microparticles, but preferably nanoparticles, i.e., diameter less than 1 micron, of active agent, coated with the biocompatible polymer, suspended in the aqueous phase. These can be injected to provide a pre-programmed release profile, with duration from a few hours to weeks or months from a single dose. Under the high shear conditions, the particles are small enough (less than a few microns) to be safe, without risk of capillary blockage or infarction; smaller sizes (less than 200 nm) can be sterile filtered for injection. The particles may be either crystalline and/or amorphous, with the latter preferred for better bioavailability. A wide variety of active agents, including therapeutic, prophylactic, and diagnostic agents, and agents of nutritional value, can be delivered in the formulation. Examples of therapeutic/prophylactic agents include analgesics, antipyretics, anaesthetics, antiasthmatics, antibiotics, antidepressants, antidiabetics, antifungals, antihypertensives, antiinflammatories, antineoplastics, antianxiety or antimigraine drugs, immunosuppressives, sedatives, hypnotics, antianginals, antipsychotics, antimania or antigout agents, antiarrhythmics, antiarthritics, anticoagulants, thrombolytics, antifibrinolytics, haemorheologic or antiplatelet agents, antiparkinson or calcium regulatory agents, antihistamines, antipruritics, antimicrobials, antibacterials, antivirals, antiinfectives, bronchodilators, hormones, , hypoglycaemics, hypolipidaemics, proteins, nucleic acids (both sense and antisense to encode proteins), erythropoietin stimulators, antiulcer, antireflux agents, antinauseants, and antiemetics. Most notable are antineoplastics and immunosuppressants; specific antineoplastic examples are adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin, methotrexate, fluorouracil, cisplatin, carboplatin, carmustine (BCNU), methyl-CCNU, etoposide, piposulphan, interferon, or camptothecin, taxol (paclitaxel), taxotere, and their derivatives; of immunosuppressants, cyclosporine, azathioprine, mizoribine, and FK506; other drugs noted are mitotane, visadine, halonitrosoureas, anthrocyclines, and ellipticine. Examples of diagnostic agents are contrast agents for ultrasound, radioactives, and magnetic resonance. Examples of nutritional agents include amino acids, sugars, proteins, carbohydrates, fat-soluble vitamins (A, D, E, K), and fats.

ADVANTAGE - Disadvantages of oral administration, including insolubility with low bioavailability, are avoided; also encapsulation protects the drug from liver ''first pass'' effects. Surfactants, as used in Cremophor and other prior art dispersants, can have allergic or even toxic side effects, e.g., myelosuppressive, if used in considerable quantities, as required for taxane type antineoplastics, limiting or preventing continuous administration. Many drugs do associate naturally with serum proteins as carriers in the body, particularly serum albumin. The present method avoids surfactants, but allows solutions containing, e.g., more than 1 mg/ml of taxol, resulting in effective total infusion volumes of less than 300 ml. This improves patient compliance; in addition, ability for continuous dosing without breaks minimises hospital stay. When the carrier is biodegradable, as with proteins, no effects are felt from the system.

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Title Terms: DELIVER; WATER; INSOLUBLE; BIOACTIVE; AGENT; SUSPENSION; COATING; AGENT; ORGANIC; PHASE; AQUEOUS; PROTEIN; SYNTHETIC; POLYMER; STABILISED; HIGH; SHEAR; NOTABLY; TAXOL
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